Remarks/Arguments

The foregoing amendments to the claims are of a formal nature and do not add new matter. Claims 28-47 were pending in this application and were rejected on various grounds. The claims have been amended for clarity and with the functional recitation " wherein said encoded polypeptide is an immunosuppressor." Support for this recitation is found in the instant specification in Example 137.

Further, claims 48-59 have been added with the functional recitation "wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors or wherein said encoded polypeptide induces chondrocyte proliferation." Support for the new claims can be found in the instant specification in Example 143 and 153. Rejections to the presently pending claims are respectfully traversed.

Priority

Applicants rely on the 'Inhibition of the mixed lymphocyte reaction' assay (Example 137) for patentable utility of subject matter relating to claims 28-47 in this case. This utility was first disclosed in International Application PCT/US00/04342, filed February 18, 2000, priority for which has been claimed in this application. Hence, the present application is at least entitled to an effective filing date of **February 18, 2000** based on results of the "inhibition of MLR" assay.

Applicants also rely on the 'gene amplification' assay (Example 143) for patentable utility of subject matter relating to claims 33-59 in this case. This utility was first disclosed in the US Provisional Application 60/162,506, filed October 29, 1999, priority for which has been claimed in this application. Hence, the present application is at least entitled to an effective filing date of **October 29, 1999** based on results of the 'gene amplification' assay.

Further, Applicants rely on the 'chondrocyte proliferation' assay (Example 153) for patentable utility of subject matter relating to claims 33-52 in this case. This utility was first disclosed in International Application PCT/US00/04342, filed February 18, 2000, priority for which has been claimed in this application. Hence, the present application is at least entitled to an effective filing date of **February 18, 2000** based on results of the 'chondrocyte proliferation' assay.

Information Disclosure Statement

Applicants submit an IDS separately enlisting references recited in the Blast report in order to be compliant with 37 C.F.R. § 1.98(a)(1). Consideration of this Information Disclosure Statement is respectfully requested.

Specification

A. The disclosure was objected to by the Examiner as containing "embedded hyperlink and/or other form of browser-executable code." The foregoing amendment to the specification which deleted all embedded hyperlinks, is believed to overcome the present objections.

B. The title of the invention has been amended to better describe the claimed invention.

Accordingly, Applicants believe that all objections to the specification have been overcome and should be withdrawn.

Claim Objections

The syntax of claims 28-47 have been amended to remove references to Figures. Thus, Applicants believe this objection has been overcome and should be withdrawn.

Claim Rejections – 35 USC § 101 and 35 USC § 112, first paragraph

A. Claims 28-47 were rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by a specific, substantial and credible asserted utility or well established utility."

7A. Claims 28-47 are also rejected under 35 U.S.C. §112, first paragraph for failing to adequately teach how to use the instant invention. Applicants respectfully disagree with and traverse the rejection to the remaining claims.

The Examiner asserts, using exemplary articles like Skolnick *et al.*, Bork *et al.*, Doerks *et al.*, Smith *et al.* and Brenner *et al.*, that there are "specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan the utility of the protein of SEQ ID NO: 271 which is only known to be homologous to various receptors." For the reasons outlined below, Applicants respectfully disagree.

Utility Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: **"If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."**

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.**

Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Further, the legal standard with respect to *in vitro* or animal model data providing pharmacological activity has been commented on in *Cross v. Iizuka*, 753 F.2nd 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985):

> "We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vitro* utility."

Furthermore, M.P.E.P. 2107.03 (III) states that:

> "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Thus, the legal standard accepts that *in vitro* or animal model data is acceptable utility as long as the data is "reasonably correlated" to the pharmacological utility described.

Arguments

The encoded PRO1410 polypeptides have utility as immunosuppressors

Without acquiescing to the propriety of this rejection, but solely in the interest of expediting prosecution in this case, Applicants submit a declaration with supportive references from the art to show that PRO1410 polypeptides have immunosuppressive activity.

Applicants submit a declaration by Sherman Fong, Ph.D. of Genentech, Inc., an expert in the field of Immunology and co-inventor of the present application, to show that there are specific immune stimulant utilities for compounds identified by an MLR assay. The Declaration

explains how the MLR reaction was performed in the instant application using peripheral blood mononuclear cells (PBMCs), which contain responder T-cells, and allogenic, pre-treated (irradiated) PBMCs, which predominantly contained dendritic cells. Further, Dr. Fong's declaration clearly states that:

> "Some PRO polypeptides do the reverse, and give inhibition of T-cell proliferation in the MLR assay. It is my considered scientific opinion that a PRO polypeptide shown to inhibit T-cell proliferation in the MLR assay where the activity is observed as 80% or less of the control, as specified in the present application, would be expected to find practical utility when an inhibition of the immune response is desired, such as in autoimmune diseases".

Accordingly, the positive results obtained in this assay clearly establish that the polypeptides encoded by the instantly claimed nucleic acids have utility as immunosuppressors. By the foregoing arguments and supportive evidence, Applicants have established that the MLR reaction is a generally recognized assay to assess immunoinhibitory as well as immunostimulatory activity. Thus, the PRO1410 polypeptides have immunosuppressive uses, for example, in the treatment of graft rejections, autoimmune diseases, etc and accordingly, one of skill in the art would know that their nucleic acids are useful as well.

Since the legal standard accepts *in vitro* as acceptable utility and the data is "reasonably correlated" to the pharmacological utility based on the discussions above, a valid case for utility has been made and would be considered credible by a person of ordinary skill in the art.

PRO1410 polypeptides also have utility in the diagnosis of cancer

As shown in Example 143, the nucleic acids encoding PRO1410 are amplified in lung and colon tumors. Although the instant application claims nucleic acids which have already been shown to have utility in gene amplification, Applicants also discuss below gene amplification utility for the encoding proteins.

Applicants submit that it is "more likely than not" for amplified genes to have increased mRNA and protein levels. Applicants submit further exemplary articles to show that, the art indicates that, generally, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. For example, Orntoft *et al.* (Mol. and

Cell. Proteomics, 2002, Vol.1, pages 37-45) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Ornitoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (Cancer Res., 2002, Vol. 62, pages 6240-45) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.,* (PNAS, 2002, Vol. 99, pages 12963-12968) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

Also enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in

approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the art of genes that do not fit within the central dogma of molecular biology, these instances are exceptions rather than the rule. In the vast majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* and the Polakis declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1410 gene, that the PRO1410 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO1410 proteins have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the protein for diagnosis of cancer.

Claimed proteins would have diagnostic utility in cancer diagnosis even if the protein were not overexpressed

Even assuming *arguendo* that, there is no correlation between gene amplification and increased mRNA/protein expression for PRO1410, which Applicants submit is not true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants submit a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression

> of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician need not treat a patient with agents that target that gene product. This not only saves money, but further prevents unnecessary exposure of the patient to the side effects of gene product targeted agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

In conclusion, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1410 polypeptide based on the gene amplification results for the nucleic acid, for example, in detecting over-expression or absence of expression of PRO1410. In fact, the art also indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Further, based on the instant disclosure, the functional recitation in the claims, one skilled in the art, at the time the application was filed, would know how to make and use the claimed polypeptides, without undue experimentation.

Thus, Applicants have demonstrated utility for the PRO1410 polypeptide as a tumor marker for lung or colon cancer that are useful in their diagnosis.

The encoded PRO1410 polypeptides also have utility based on results in chondrocyte proliferation assay

Applicants further rely on the chondrocyte proliferation assay (Example 153) for support of patentable utility.

It was well known at the effective filing date of the present application that chondrocytes play a key role in the synthesis and maintenance of the articular cartilage, which in turn is essential to normal joint function. Unfortunately, compared to many other tissues, articular cartilage essentially lacks the ability to regenerate following injury. One way of achieving cartilage repair, for example in osteoarthritis, is to harvest human articular chrondrocytes (HACs) from non-affected, healthy areas of the joint to be repaired. The HACs are subsequently grown in monolayer cell culture in order to produce sufficient amount of cells to fill the articular defect. Chondrocytes found in healthy joints have a round shape, and express high levels of extracellular matrix molecules, such as aggrecan, type II collagen, and link protein. In contrast, monolayer cultures of chondrocytes produce dedifferentiated fibroblast-like structures, similar to those found in the cartilage of aging and arthritic joints. (See, e.g. Zhang et al., *Experimental Cell Research* 263:33-42 (2001) – copy enclosed). Accordingly, agents that are capable of inducing chondrocyte proliferation, as evidenced by proper growth and differentiation of chrondrocytes in monolayer cell cultures, can be used in the treatment of joint diseases using a tissue engineering approach (See, e.g. Schnabel et al., Osteoarthritis and Cartilage, 10(1):62-70 (2002) – copy enclosed). In addition, molecules capable of inducing chondrocyte proliferation and/or redifferentiation are promising drug candidates to repair aging or arthritic joints, for example, in joints where the chondrocytes have been dedifferentiated.

As set forth in M.P.E.P, 2107 II (B) (1), if the applicant has asserted that the claimed invention is useful for any particular practical purpose, and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility should not be imposed. The logic underlying the asserted utility in the present case is not inconsistent with general knowledge in the art, and would be considered credible by a person skilled in the art. It is, of course, always possible that an invention fails on its way of development to a commercial product. Thus, despite recent advances in rational drug design, a large percentage of drug candidates fails, and never makes it into a drug product. However, the USPTO is not the FDA,

the law does not require that a product (drug or diagnostic) be currently available to the public in order to satisfy the utility requirement.

Applicants refer to the statement in Example 153, the description of the chondrocyte proliferation assay that "A positive result in the assay is obtained when the fluorescence of the PRO polypeptide treated sample is more like that of the positive control than the negative control." Fluorescence determination wherein the readout is compared to controls is well known in the art. Thus, these indica are truly determinative of the proliferation of chondrocyte cells.

In view of the foregoing arguments and submitted evidence, the use of PRO1410 polypeptides constitutes several "real world" uses. Accordingly, one of skill in the art would know that the nucleic acids encoding the polypeptides also have utility. Thus, the Examiner is respectfully requested to reconsider and withdraw the present rejections under 35 U.S.C. §101 and §112, first paragraph.

Claim Rejections – 35 USC § 112, first paragraph

B. Claims 28-47 are also rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and /or use the invention.

The Examiner pointed out that the deposit of biological material made under the Budapest Treaty for enablement of the current invention needs the current address of the ATCC and a declaration or statement stating that all restrictions imposed by the depositor on the public be irrevocably removed. Applicants submit that requisite assurances have been added into the specification to remove, irrevocably, all restrictions imposed by the depositor on the availability of deposited material to the public upon the granting of the pertinent U.S. patent. Accordingly, this rejection should be withdrawn.

C. Claims 28-47 are also rejected under 35 U.S.C. §112, first paragraph because, according to Examiner, "the specification, while being enabling for SEQ ID NO: 271 and 270, does not reasonably provide enablement for polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity to SEQ ID NO:271, ATCC No 203277, its extracellular domain or fusion proteins. Applicants respectfully traverse this rejection.

Initially, references to the extracellular domain have been removed from the instant claims hence, this rejection is moot with respect to this subject matter. Furthermore, as discussed earlier, the encoded PRO1410 polypeptides have several utilities based on the MLR assay (as an immunosuppressor), on the gene amplification assay (for the diagnosis of lung or colon cancer) and on the chondrocyte proliferation assay. The claimed genus in the presently amended claims recite these functional recitations and hence the claimed molecules are defined by sequence as well as functional identity. One skilled in the art would readily understand and appreciate, based on the general knowledge in the art and the disclosure of the present application, how to make and use the claimed invention at its effective filing date. Therefore, Applicants request reconsideration and withdrawal of this rejection.

Claim Rejections - 35 USC § 112, first paragraph- written description

Claims 28-47 are rejected under 35 U.S.C. 112, first paragraph because allegedly, the subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing.

As discussed above, specific utilities have now been asserted for the presently pending claims that recite functional recitations "wherein said polypeptide is an immunosuppressor" and "wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors or said polypeptide induces chondrocyte proliferation." Since the claims are drawn to a genus of polypeptides defined both by sequence and functional identity, it would have been obvious to one skilled in the art at the effective priority date, in view of Applicant's possession of the nucleic acid of SEQ ID NO:270 and the PRO1410 (SEQ ID NO:271), that the Applicant possessed these obvious variations and adaptations of SEQ ID NO:271 at the time of filing.

Thus this rejection should be withdrawn.

Claim Rejections – 35 USC § 112, second paragraph

A. Claims 28-47 were rejected under 35 U.S.C. §112, second paragraph for being indefinite. The Examiner alleges that it was not clear whether or not the protein encoded by the polynucleotide of the present invention was a soluble protein nor was it disclosed as being

expressed on a cell surface. The recitation "extracellular domain" and "lacking its associated signal sequence" was also indefinite.

Without acquiescing to the propriety of this rejection and without limitations to pursuing this subject matter in future applications, merely to expedite prosecution in this case, Applicants have canceled references to "the extracellular domain" in the pending claims.

B. Claims 41-43 are vague and indefinite since the claims recite "hybridizes" without recitation of any conditions.

Applicants have canceled claims 41-43 without prejudice or disclaimer. Further, new claims 53-59 now recite the hybridization conditions used. Accordingly, this rejection should be withdrawn.

Claim Rejections - 35 USC § 102

Claims 28-47 are rejected under 35 U.S.C. §102(b) as being anticipated by Ashkenazi et al. (WO 00/53758, pub date 9/14/00).

The PRO1410 sequence and its encoding nucleic acid were first disclosed in U.S. Provisional application 60/101476, filed 9/23/1998, priority for which has been claimed in the instant application. Furthermore, as discussed earlier, specific, substantial and credible utilities for PRO1410 have been asserted by Applicants at least on October 29, 1999 and February 18, 2000. Since all of these dates precede the publication date of Ashkenazi *et al.*, it is not prior art under 35 U.S.C. § 102(b) or any other section of 35 USC § 102.

Therefore, Applicants request that this rejection be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2830P1C58). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: September 15, 2004

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